REMARKS

Claim 1 is the only pending claim.

Reconsideration of the above-captioned application in light of the following discussion is respectfully requested.

Claim 1 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for the prevention of inflammation and, therefore, the scope of the claimed invention for prevention of inflammatory diseases by using chemical compounds was thought to be too broad.

Applicants respectfully submit that the specification of the presently pending application does provide reasonable enablement for the scope as set forth in the presently pending claim. Applicants respectfully direct the Examiner's attention to page 8, Example 3, of the application wherein the GABA analog, pregabalin, was administered both before the induction of inflammation and after the development of inflammation in the animal model. The results of this experiment are set forth beginning on page 10, line 15, of the specification through page 11, line 11. The results demonstrated that rats infused with pregabalin or its R-isomer through the spinal cord for 1.5 hours before injection of arthritis-inducing agents (kaolin and carrageenan) resulted in no secondary thermal hyperalgesia four-hours post-injection (see Figure 1, top panel).

The infusion of pregabalin or its R-isomer into the spinal cord for 1.5 hours before the induction of arthritis also significantly reduced the amount of swelling typical after the injection of kaolin and carrageenan into the knee joint by approximately 30% (see Figure 1, middle panel). Further, pre-treatment with pregabalin or its R-isomer prevented the development of abnormal paw posture indicative of spontaneous pain (see Figure 1, bottom panel).

Referring to page 12, Example 4, gabapentin, another GABA analog, was evaluated in a similar assay and was also shown to be effective in both preventing and

reversing the effects of kaolin/carrageenan knee joint inflammation, secondary heat hyperalgesia, and spontaneous pain-related behaviors.

Accordingly, Applicants respectfully submit that the data set forth in Examples 3 and 4 demonstrate that GABA analogs, such as gabapentin and pregabalin, are effective in both preventing and reversing the effects of kaolin/carrageenan knee joint inflammation on secondary heat hyperalgesia and spontaneous pain-related behaviors. Applicants respectfully submit that the specification contains sufficient enablement for claims covering the prevention of inflammation and that the claims are commensurate in scope with the enablement provided in the specification. Accordingly, Applicants respectfully submit that the rejection of Claim 1 under 35 U.S.C. §112, first paragraph, has been overcome.

Claim 1 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Satzinger et al. (U.S. 4,024,175) and further in view of Nagai (JP 60036413). Reconsideration of the rejection under 35 U.S.C. §103(a) as unpatentable over Satzinger et al. and further in view of Nagai is respectfully requested.

The Examiner alleges that Satzinger et al. teach (column 2, lines 27-30) that the GABA analogs containing a cyclic alkyl 5-7 membered ring substituent on the delta (#3) carbon atom of GABA can be used to treat cranial trauma. The Examiner states that Nagai allegedly teaches that GABA itself treats inflammatory diseases (see abstract, last paragraph, line 3).

The abstract of the Nagai patent discloses GABA and salts of GABA accelerate "the formation of granulation tissue, and as a result accelerates the cure of inflammation."

Pending Claim 1 defines a method of using GABA analogs and the pharmaceutically acceptable salts thereof, for preventing and treating inflammatory diseases.

"GABA" stands for gamma amino butyric acid. A salt of "GABA" is simply a salt (*e.g.*, sodium) of gamma amino butyric acid. The presently claimed invention does not include the use of salts of GABA. Rather, the methods of the instant claimed invention employ specifically defined analogs of GABA, including certain preferred analogs that are defined in the instant specification on page 4 at lines 2-11. The instant claimed method clearly discloses more than one GABA analog. Further, Hackh's Chemical Dictionary, 4th ed., J. Grant ed., McGraw-Hill Book Company, New York, 1972, p. 44 (copy enclosed) defines the term "analogs" as being compounds with similar electronic structures but different atoms. Thus, Claim 1 defines a method of preventing and treating inflammatory diseases comprising administering to a subject in need of treatment an anti-inflammatory amount of a compound selected from a certain group of compounds that provide discrete bioactive agents *in vivo* that possess similar electronic structures but different atoms.

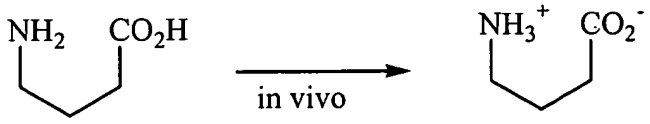
Further, one of ordinary skill in the art would expect that *in vivo*, the bioactive form of GABA derived from administration of salts of GABA would be identical to the bioactive form derived from administration of GABA itself (*i.e.*, the corresponding parent free acid compound). This is so because the bioactive form would be delivered to sites of inflammation dissolved in mammalian physiologic systems such as blood and synovial fluid, and it is well known that these systems are buffered. A buffered system, by definition, converts a free acid or free base form of a parent compound and corresponding acid/base salts thereof to the same form in solution. (The instant subjects are mammals, as described on page 5 at line 24.) Accordingly, one of ordinary skill in the art would know that administration of GABA, or a salt thereof, to a mammal would provide a single bioactive form of GABA *in vivo*.

Further on page 4 at line 17, the phrase "Pharmaceutical compositions of a GABA analog or its salts are produced . . ." distinguishes that even a salt of a GABA analog is not a "GABA analog", as that term is now presently defined.

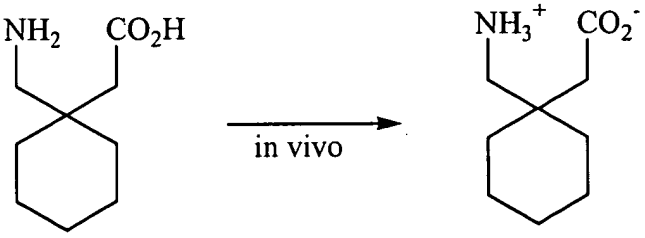
Accordingly, GABA analogs are compounds that, when administered to a mammal according to the method of the present invention, provide compounds *in vivo* that have similar electronic structures but different atoms when compared to the bioactive form of GABA. Administration of GABA itself (gamma amino butyric acid), or a salt thereof, would provide a bioactive agent *in* vivo that would clearly be different from the bioactive form provided by administration of an analog of GABA such as gabapentin, or a salt thereof.

The above remarks are illustrated in the scheme below, which assumes physiological pH 7.4.

Administered form → Possible bioactive form (assuming physiological pH 7.4)



GABA (or a salt thereof)



gabapentin (or a salt thereof)

In the scheme, there is one predominant bioactive form of GABA, and salts thereof, and one predominant bioactive form of gabapentin, and salts thereof. (Predominant because no acid-base reaction is complete in solution.) Further, the bioactive form of GABA, and salts thereof, shares some, but not all, atoms and bonds with the bioactive form of gabapentin, and salts thereof. Clearly, salts of GABA are not analogs of GABA as that term is now defined.

Accordingly, at the time the instant invention was made, GABA analogs were not disclosed in the Nagai reference to be effective in treating inflammation. Further, as the Examiner admits, it was known at the time the invention was made that GABA analogs did not bind to the GABA receptor. Thus, while it was known that both GABA and GABA analogs were effective in prevention of seizures, it was also known that GABA analogs such as gabapentin worked via a biochemical mechanism different from binding to GABA receptors. To one of ordinary skill in the art, this meant that GABA pharmacology was not predictive of the pharmacology of GABA analogs. Accordingly, the Nagai reference would lead one of ordinary skill in the art away from the presently claimed method simply on the basis of these different biochemical mechanisms. Those possessing ordinary skill in the art would not have been expected to screen available analogs of GABA to see if the analogs possessed the same anti-inflammatory properties as GABA itself. Therefore it would not have been obvious to one of ordinary skill in the art to expect Satzinger's compounds to be effective for treating inflammation in view of Nagai. Moreover, to suggest that the skilled artisan would be expected to "screen" for active compounds suggests it might be obvious to try various compounds, but this is not the standard for obviousness under 35 U.S.C. §103(a).

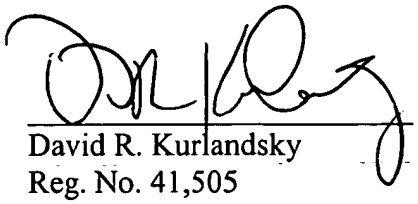
In view of the above remarks, Applicants respectfully submit that the rejection of Claim 1 under 35 U.S.C. §103(a) has been overcome. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 1 stands rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of United States Patent No. 6,329,429. Applicants submit herewith a timely filed terminal disclaimer in compliance with 37 CFR §1.321(c) to overcome this rejection.

In view of the foregoing remarks, reconsideration of the rejection and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this Communication to our Deposit Account No. 23-0455.

Respectfully submitted,



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Attachments - Hackh's Chemical Dictionary, 4th ed., J. Grant ed., McGraw-Hill Book Company, New York, 1972, p. 44
Terminal Disclaimer

HACKH'S CHEMICAL DICTIONARY

Library of Congress Catalog Card Number 61-18726

07-024064-7

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the seeds of *Anagyris foetida* (Leguminosae). A brittle, resinlike mass, b.245. It resembles cytisine and sparteine in structure. **a. hydrobromide.** $C_{15}H_{18}ON_2 \cdot HBr = 323.3$. Yellow crystals, m.265, soluble in water; a heart stimulant.

anahemin. A liver polypeptide responsible for the maturation of the red blood cells in the bone marrow.

analcime. Analcite.

analcite. $NaAlH_2Si_2O_7$. Analcine. A white, isometric native sodium aluminum silicate zeolite, deposited in high-pressure boilers.

analeptic. (1) A drug that restores health. (2) More specifically, a drug that stimulates the central nervous system, and especially the respiratory and vasomotor centers.

analgen(e). (1) $C_7H_5O \cdot NHC_6H_3(OEt):C_3H_3N = 292.24$. 5-Benzamido-8-ethoxyquinoline, benzanalgen, quinalgene, labordin. Colorless crystals, m.208, insoluble in water; an antipyretic, antirheumatic, and analgesic. (2) $C_{13}H_{14}O_2N_2 = 230.12$. 5-Acetylamino-8-ethoxyquinoline. Colorless crystals, m.155.

analgesic. A drug that relieves pain without causing loss of consciousness, either by direct action on nerve centers (brain), or by diminishing the conductivity of the sensory nerve fibers; e.g., the use of nitrogen dioxide in obstetrics.

analgesine. Antipyrine.

analgic. Painless.

analgin. Creolin.

anallachrom. Esculin.

analogs, analogues. Analogous series. Compounds with similar electronic structures but different atoms; as, *isosteres* and *isologs*.

analogy. A similarity or a likeness in properties. Cf. *homology, isology*.

Analoids. Patented tablets containing exact quantities of reagents, used in chemical analysis. Cf. *Fixanol*.

analyser. Analyzer.

analysis. (1) Assay. The determination, detection, or examination of a substance. (2) Breaking down or splitting into simpler constituents. (3) The reverse of synthesis. **bio-** (1) The detection of substances with the aid of microorganism; e.g., by the selective action of yeasts on sugars; or by ascertaining the minimum amount of the sample under test that will inhibit growth of an organism or produce specific disease symptoms in an experimental animal. (2) The determination of the strength of substances (as, hormones) from their effects on animals. **activation-** The identification of elements from the characteristic radiations they emit on returning to their normal states after bombardment by high-energy fast neutrons. **biochemical-** The chemical examination of biological material. **blowpipe-** The detection of metallic elements and acid radicals by means of the blowpipe. **chromatographic-** See *chromatographic*. **clinical-** The examination of body fluids and tissues for the diagnosis of diseases. **colorimetric-** The quantitative a. of substances by means of the color intensity of their reaction products. **complexometric-** See *complexometric*. **conductometric-** See *conductometric analysis*. **differential thermal-** Following a chemical reaction from the difference in temperature between the substance being examined and a thermally inert standard when both are heated similarly. **diffusion-** See *diffusion*. **dry-** A. without the use of solutions. **electro-** See *electrodeposition* analysis. **elementary-** The determination of the constituents of an organic compound by combustion; e.g., C as CO_2, H as H_2O. **gas-** A. of gas mixtures by measuring the volumes before and after treatment with selective absorbing agents. **gravimetric-** The determination of the composition of a substance by weighing its constituents directly or indirectly. **iodimetric-** Titration of oxidizing substances with a standard sodium thiosulfate and acid potassium iodide solutions. **mechanical-** See *mechanical*. **mechanochemical-** Qualitative microanalysis based on the color produced when solid reactants are rubbed together in a mortar. **micro-** (1) Identification of substances under the microscope, e.g., starch. (2) The identification of characteristic reaction products (precipitates, crystals) with the microscope. (3) Modifications on the small scale of the processes of quantitative analysis. **m.biological-** q.v. **narco-** q.v. **nephelometric-** Measurements of turbidity to determine the amounts of precipitates. **organic-** *Elementary* analysis. **proximate-** The determination of the chemical nature of the active constituents of a sample; e.g., the alkaloids in drugs. **qualitative-** The detection of the kind or nature of an element or compound in a substance. **quantitative-** The determination of the amount or quantity of an element or compound in a substance. **rational-** See *rational*. **screen-** See *screen*. **spectroscopic-** See *spectroscopic*. **spectrum-** The detection of elements and binary compounds by their characteristic radiations as observed through the spectroscope. **spot-** See *spot*. **submicro-** A. concerned with quantities of 20–50 γ. **technical-** Practical or empirical methods used in industry for evaluating materials. **thermodynamic-** The measurement of a component of a gas mixture by passing the mixture through a calibrated orifice for a known time, into an evacuated vessel, and measuring the increase in pressure in the latter **ultimate-** Elementary a. **volumetric-** The determination of elements and compounds in a substance by titration with standard solutions. **wet-** An a made with solutions. See also *bead tests, biological assay, calorimetry, chromatography, colorimetry, electrolysis, flame tests, reactions, spectroscopy, thermal, titration*.

analytical. Pertaining to analysis. **a. balance.** See *balance*. **a. chemistry.** See *chemistry*. **a. metabolism.** Catabolism. **a. reactions.** The characteristic reactions of elements or ions, used for the identification or determination; e.g., precipitate formation, color changes. **a. weights.** The standardized weights of an analytical balance.

analyzer. (1) A device which indicates a certain condition, change, or phenomenon. (2) The nicol prism of a polariscope nearest to the eyepiece. (3) The first tower of a coffee still. **curve-** device for determining the slope of a graph. **micropolar-** An optical attachment for a microscope for the determination of polarization in crystals. **polarization-** The nicol prism in the polariscope nearest to the eye. Cf. *polarizer*.

anamirtin. (1) $C_{10}H_{16}O_{10}$. A glucoside from the fruits of *Anamirta paniculata*. (2) $C_{19}H_{24}O_{10}$.